UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/088,139	12/17/2002	Anne Eckert	43551	1457

5487 7590 04/04/2006

ROSS J. OEHLER
AVENTIS PHARMACEUTICALS INC.
1041 ROUTE 202-206
MAIL CODE: D303A
BRIDGEWATER, NJ 08807

EXAMINER	
HAMA, JOANNE	
ART UNIT	**PAPER NUMBER**
1632	

DATE MAILED: 04/04/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/088,139	ECKERT ET AL.	
	Examiner	Art Unit	
	Joanne Hama, Ph.D.	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 January 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant filed a response to the Non-Final Rejection of July 14, 2005 on January 13, 2006. Claim 1 is amended.

Claims 1-8 are under consideration.

Withdrawn Rejections

35 U.S.C. § 101

Applicant's arguments, see page 3 of Applicant's response, filed January 13, 2006, with respect to the rejection of claims 1-5 being directed to non-statutory subject matter have been fully considered and are persuasive. Applicant has amended the claims to transgenic "non-human" animal. The rejection of claims 1-5 has been withdrawn.

Maintained Rejections

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 1-8 remain rejected under 35 U.S.C. 101 because the claimed invention lacks patentable utility for reasons of record, July 14, 2005.

Response to Arguments

Applicant's arguments filed January 13, 2006 have been fully considered but they are not persuasive.

Applicant indicates that the Office Action acknowledges that the mice described in the specification exhibit higher levels of apoptosis in T-lymphocytes. The mice, therefore, are useful at least at this level, e.g. as a model to monitor apoptosis. While the Applicant provides this argument, it is not found persuasive because merely indicating a phenotype with no known correlation or relationship to a human disease or disorder is not a readily apparent use of the mice described in the specification. It should be pointed out that the appearance of mere indistinct words in a specification or a claim, even an original claim, does not necessarily satisfy that requirement. ...A description of an anti-inflammatory steroid, i.e., a steroid (a generic structural term) described even in terms of its function of lessening inflammation of tissues fails to distinguish any steroid from others having the same activity or function. A description of what a material does, rather than of what it is, usually does not suffice. [*Reagents of the Univ. of Cal. v. Eli Lilly & Co., Inc.*], 119 F.3d[1559,] 1568 [43 USPQ2d 1398] [Fed. Cir. 1997) ("*Lilly*")] .... The disclosure must allow one skilled in the art to visualize or recognize the identity of the subject matter purportedly described. *Id.* In other words, it is not sufficient to claim a transgenic mouse comprising in its genome, a transgene construct that expresses a multimutated form of presenilin 1, wherein said transgenic mouse exhibits certain phenotypes. As such, while the specification indicates that the mice comprising a transgene that expresses a protein encoding 5 point mutations of human PS 1 exhibits apoptosis in T lymphocytes, nothing in the art or specification

provide any guidance that there is a relationship between mutant PS1, apoptosis in T lymphocytes, and Alzheimer's disease. Thus, the mice described in the specification would need to be further characterized to identify or reasonably confirm a "real world" context of use and thus the mice described in the specification do not have specific and substantial use.

Applicant indicates further utility of the mice described on page 6, parag. 2 of the specification and indicates the examples as demonstrating that the animals of the instant invention cellular impairments found in Alzheimer's disease (AD) and exhibit increased sensitivity to apoptosis such as found in AD (Applicant's response, pages 3-4). While page 6, parag. 2 indicates that the mouse model exhibits symptoms associated with AD (specification, page 6, line 3), nothing in the specification indicates that the mice have AD e.g. amyloid plaques, and thus, it remains unclear whether a relationship exists between mutant forms of PS1, AD, and apoptotic T lymphocytes and if one does, what is the biological relationship between PS1, AD, and apoptotic T lymphocytes.

Thus, claims 1-8 remain rejected under 35 U.S.C. 101.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-8 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention for reasons of record, July 14, 2005.

Response to Arguments

Applicant's arguments filed January 13, 2006 have been fully considered but they are not persuasive.

Applicant indicates that the Office Action acknowledges that the specification teaches several embodiments, but alleges lack of enablement, based on the false allegation that nothing in the art or specification teaches a relationship between apoptosis and PS1, i.e., that no guidance is provided that certain mutations or amino acid combinations are associated with apoptosis (Applicant's response, page 4, 2nd parag. under "Rejections under 35 U.S.C. 112"). In response, the Examiner was not questioning whether the mice described in the specification exhibited apoptosis in T lymphocytes or not. Rather, the Examiner indicated that nothing in the specification or the art provide guidance that there is a biological relationship between apoptosis in T lymphocytes, AD, and a mutant form of PS1, such that the gene of interest, disease, and phenotype are correlated with each other. Again, merely asserting that there is a T lymphocyte phenotype exhibited in the mice comprising a mutant form of PS1 does not provide guidance for using the claimed mice. Rather, a biological relationship between

the phenotype, disease, and gene need to be established in order to use the claimed animal as a model of disease.

Regarding the issue of the rejection relating to promoters, while the Office Action did focus on not all promoters being functional across multiple animals species, the point that the Examiner was making about transgene constructs in general was that one transgene construct does not predictably have activity in other species of animals (Office Action, page 7, 2nd parag.). One of the reasons for this unpredictability stems from the fact that heterologous promoters do not behave predictably in other species of transgenic animals. While it is understood that the skilled artisan is aware of a variety of promoters, selection of bases, and uses (Applicant's response, page 5, 2nd parag.), it should be pointed out that an artisan is not enabling for the full breadth of all types of promoters that can be used any non-human animal (including insects), as broadly encompassed in the claims. That is, nothing in the specification or the art provides guidance for an artisan to obtain any promoter and know whether it has activity in all types of non-human animals as broadly encompassed in the claims. As such, the scope of the claimed invention is limited to a transgenic mouse.

Regarding the issue of the rejection relating to insertion site of a transgene, the Applicant indicates that interruption of a gene by insertion of genetic material therein may inactivate the interrupted gene and result in a particular phenotypic expression of the cell or progeny thereof. However, the chance that in some embodiments an additional phenotypic pattern may be obtained does not detract from the fact that the transgene described in the present invention has its own demonstrated phenotypic

pattern (Applicant's response, page 5, 3rd parag.). In response, the point that was being made was that due to the copy number and sites in which the transgene inserts in the genome is another reason for the unpredictability in producing a transgenic non-human animal. It is unclear whether any phenotype corresponding to the transgene would be exhibited by the transgenic non-human animal comprising a transgene construct of interest. In the instant situation, it is unclear whether other transgenic non-human animals would also exhibit apoptosis in T-lymphocytes. In light of the fact that some transgene constructs may not have any activity in heterologous animal species (discussed above) and that it is unclear where and how many copies of a transgene construct insert into the genome of a transgenic animal, it is unclear whether an artisan can predictably obtain any transgenic non-human animal model that exhibits apoptosis in T-lymphocytes.

Regarding the issue of the rejection relating to renewable tissue, the Applicant indicates that while the instant specification does not provide an example relating to every tissue and cell type that can be found in an organism, a working example is provided. Applicant indicates that the Office Action provides no evidence that any other tissue would not similarly work or that the skilled artisan would require undue experimentation to practice the claimed invention. Applicant also indicates that the skilled artisan is well aware that a viable cell is necessary requisite for apoptosis, therefore a myriad of cell organelles and structures including a nucleus must be in common (Applicant's response, page 6, 2nd parag.). In response, the issue at hand was not whether an artisan had the tools used to detect apoptosis, but whether the

specification taught a broad scope of apoptosis being exhibited in any "renewable tissue." The point here is that nothing in the art or specification indicates a biological relationship between PS1 and apoptosis in other renewable tissues such as liver, skin, and the lining of the intestine such that the specification enables the artisan to observe apoptosis in these tissues. While the specification provides guidance for mice exhibiting apoptosis in T-lymphocytes, the specification does not provide guidance for the broad scope of any renewable tissues.

Regarding the rejection of the claims and neurodegenerative diseases, Applicant indicates that claims 6 and 8 are the only claims that recite neurodegenerative diseases. Applicant indicates that the Office Action acknowledges that the specification does teach a relationship between Parkinson's and PS 1. Applicant indicates that it is a misunderstanding of the invention, as the Office Action states, "an artisan does not know what symptoms of Alzheimer's disease one should monitor when screening for compounds which are used to treat Alzheimer's disease" as the present invention provides a means of using a peripheral tissue or a cell as a surrogate for complex analysis of Alzheimer's symptoms (Applicant's response, page 7, 2nd parag.). In response to the "relationship between Parkinson's and PS1," this statement in the Office Action was a typographical error. The sentence should have read, "...other than Alzheimer's disease has a relationship with PS1 (Office Action, page 14, line 2)." That is, the specification and art teach a relationship between PS1 and Alzheimer's in humans. How this relates to the following sentence in the Office Action, "nothing in the specification teaches that the transgenic mouse expressing PS15M has any symptoms

associated with Alzheimer's disease," is that while the mice described in the specification exhibit apoptosis in T lymphocytes, nothing in the specification indicates that the claimed mice also exhibit Alzheimer's disease, nor is there anything in the specification that indicates a biological relationship between PS1 and apoptosis in T-lymphocytes. Regarding the issue that the present invention provides a means of using a peripheral tissue or a cell as a surrogate for complex analysis of Alzheimer's symptoms, nothing in the specification teaches a biological relationship between mutations in PS1 and apoptotic T lymphocytes such that an artisan would know that there is a distinct phenotype caused by the presence of mutant PS1 in the cell. Similarly, in the case that the claimed invention is used in a method for the treatment of neurodegenerative diseases, nothing in the specification provides guidance as to what relationship PS1 has with other neurodegenerative diseases nor is there guidance as to any biological relationship between apoptotic T lymphocytes and neurodegenerative disease such that use of the claimed transgenic non-human animals would be readily available. Applicant's response also indicates that the identified compounds may initially be intended for treatment of neurodegenerative disease, not all identified compounds will necessarily be used to treat humans (Applicant's response, page 7, 2nd parag., lines 13-16). Regarding this issue, nothing in the specification indicates what non-human diseases were intended to be encompassed by the claimed invention.

For these reasons, claims 1-8 remain rejected under 35 U.S.C 112, 1st parag.

Claims 1-8 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention for reasons of record, July 14, 2005.

Response to Arguments

Applicant's arguments filed January 13, 2006 have been fully considered but they are not persuasive.

Applicant indicates that while the Office Action asserts that the specification "does not teach how to make any multimutant PS1, such that the mutant PS1 has a role in increasing PS1 has a role in increasing apoptosis in peripheral tissue," Applicant indicates that the specification in fact does teach that the PS1 gene is associated with apoptosis. It is well known in the art how to find, isolate and mutate analogous and homologous genes. In response, while the art generally provides guidance as to possible ways of identifying homologs or analogous gene (e.g. through a hybridization screen), the art also indicates that the genes isolated this way may comprise regions common to the probe of hybridization, but does not mean that the gene obtained via hybridization is necessarily a homolog. To obtain a homolog, an artisan would need structural/functional information of the gene to be isolated. While the specification teaches human PS1 and mutant forms of human PS1 which are associated with human AD, nothing in the art or specification provide examples (structural/functional guidance)

of heterologous PS1 genes from other species of animals and nothing in the art or specification provide guidance of mutations of heterologous PS1 which result in AD. For this reason, an artisan cannot reasonably obtain any PS1 gene and any mutant of PS1 which result in AD. Applicant indicates that the issue of written description set forth in this rejection was whether the inventors possessed the claimed invention. What the skilled artisan envisions has no place in this type of rejection (Applicant's response, page 8, 2nd parag., lines 17-19). In response, a skilled artisan would need to now what structural/functional characteristics comprise PS1 and mutant PS1 because a skilled artisan would need to know what characteristics of PS1 and mutant PS1 are required for the claimed invention to work. Applicant indicates that nowhere in the patent statutes is there a requirement that every possible embodiment of an invention be demonstrated or envisioned. In response, while the Applicant need not disclose every homolog of PS1 in order to meet the written description requirement, the specification must provide guidance for an artisan to practice the claimed invention for its breadth. The claims are to any species of mutant PS1. This means that the specification and/or the art must provide guidance such that an artisan can arrive at the claimed invention. Nothing in the specification or art provides guidance, other than human PS1 comprising 5 point mutations in mouse (M is substituted for L at position 146 of the human sequence, H is substituted for R at position 163 of the human sequence, A is substituted for E at position 246 of the human sequence, L is substituted for V at position 286 of the human sequence, and C is substituted for Y at position 410 of the

human sequence), as to what characteristics comprise mutant PS1 such that its expression in any heterologous animal will result in apoptotic T lymphocytes.

For this reason, claims 1-8 remain rejected under 35 U.S.C. 112, 1st parag.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 4 remains rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention for reasons of record, July 14, 2005.

Response to Arguments

Applicant's arguments filed January 13, 2006 have been fully considered but they are not persuasive. While Applicant indicates that claim 5 depends from claim 4, the "or" must apply across the entire list, not just to the ultimate member of the group, the Examiner does not find this persuasive. The claim still reads as though there are either 13 or 14 mutations in the PS1 gene. Writing the claim as a Markush group would remedy the problem.

Conclusion

No claims allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joanne Hama, Ph.D. whose telephone number is 571-272-2911. The examiner can normally be reached Monday through Thursday and alternate Fridays from 9:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, Ph.D. can be reached on 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight

(EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public. For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

JH

ANNE M. WEHBE' PH.D
PRIMARY EXAMINER